REMARKS

Claims 3-6 and 19-21 are pending in the subject application. By this Amendment, applicants have canceled claims 19-21 without disclaimer or prejudice to applicants' right to pursue the subject matter of these claims in this or in another application. Applicants have also amended claims 3 and 5, and added new claims 22-28.

The amendments to claims 3 and 5 are supported in the specification at, *inter alia*, page 20, lines 26-29; page 24, lines 22-25; Figure 3A; and line 33 to page 25, line 2. Thus, these amendments do not raise any issue of new matter. New claims 22-28 are fully supported in the specification as follows: Claims 22 and 24: page 22, lines 22-29; page 23, lines 16-24; page 24, lines 22-25; Figure 3; page 31, lines 17-19; Claims 23 and 25: page 20, lines 26-27; page 24, lines 29-33; Figure 3B; Claim 26: page 12, lines 9-14; page 25, line 24 to page 26, line 1; page 31, lines 17-19; Claim 27: page 12, lines 14-18; and Claim 28: page 12, lines 20-25; page 25, line 24 to page 26, line 1; page 31, lines 17-19. Thus, these new claims also do not raise any issue of new matter. Accordingly, applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claims 3-5 and 22-28, as amended, will be pending and under examination.

The Invention

The invention claimed in the subject application is directed to a method of treating a subject afflicted with cardiovascular disease, which comprises administering to the subject at least 4 mg/day of a compound per kg of the subject's body weight, which compound increases intracellular cyclin-dependent kinase inhibitor p27 activity, thereby treating the subject's

cardiovascular disease. The invention also provides a method of inhibiting tumor metastasis in a subject, which comprises administering to the subject at least 4 mg/day of a compound per kg of the subject's body weight, which compound increases intracellular cyclin-dependent kinase inhibitor p27 activity, thereby inhibiting tumor metastasis. In further embodiments, the compounds which inhibit cell migration by increasing $p27^{kip1}$ activity are rapamycin or C3 exoenzyme.

Rejections under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 3-6 and 19-21 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner noted applicants' assertion that the steps required for identifying the chemical compound specified in the claimed methods are described in the specification, and that the use of this compound, not its "making," is all that is required to practice the claimed invention. The Examiner also noted applicants' contention that the application of a method of treatment of a human, based on the teachings of a method of treating a non-human animal, is not a requirement of patentability. The Examiner stated that these points of view and arguments have been carefully considered and found partially persuasive.

In this regard, the Examiner conceded that applicants' assertion concerning the requirement of patentability in the context of non-human animals and humans is true. The Examiner also stated that, while applicants set forth guidelines in the specification for the identification of compounds, the crux of the issue is the

unpredictability in the art of administering undefined and uncharacterized compounds for the treatment of cardiovascular disease and cancer. The Examiner further stated that although there are some compounds such as rapamycin (as disclosed in the specification) that increase p27 activity, thereby alleviating and inhibiting cardiovascular disease and tumor metastasis, respectively, the broad genus of compounds referred to in the claimed invention can not predictably do the same.

The Examiner stated that, for instance, peroxisome proliferators-activated receptor γ (PPARγ) ligands have been identified as compounds that increase the expression of $p27^{kip1}$. The Examiner also stated that these compounds have been noted to exhibit anticancer activity, but that, however, they stimulate cancer formation as well (citing the abstract and Table 4 on page 6 of Koeffler [2003] Clinical Cancer Research 9: 1-9). The Examiner contended that this evidence underlines the unpredictability of the art. The Examiner asserted that the broadly described molecules may not maintain the activities and function as proposed in the specification, and that in the absence of an established role of the broad chemical compounds in targeted treatment of cancer and cardiovascular diseases, it is impossible to predict what, if any, therapeutic effect the administration of any of these molecules would have. The Examiner also asserted that there is insufficient data or established precedent presented that would lead one of skill in the art to believe that the broadly described compounds would be able to function as the methodology dictates, i.e., to inhibit tumor metastasis.

The Examiner acknowledged that it is clear from the Figures that the administration of rapamycin *in vitro* and *in vivo* produced effects such as significant inhibition of smooth muscle cell (SMC) migration. The Examiner also stated that there is, however, insufficient evidence that the broadly described

compounds would yield such a result. The Examiner further stated that the analysis established on pages 4-5 of the Final Office Action, as well as in the previous Office Action, sustains her position that there appears to be no nexus between applicants' broadly claimed method of treating a subject affected with cardiovascular disease and tumor metastasis and the administration of a broad genus of undefined chemical compounds.

The Examiner also stated that the specification provides insufficient guidance with regard to administering a plethora of compounds which increase intracellular cyclin-dependent kinase inhibitor p27 activity for the treatment of disorders. The Examiner further stated that the specification also does not present sufficient working examples, which would provide guidance and a significant level of predictability to one skilled in the art, to use these compounds with a reasonable expectation of success. The Examiner concluded that in view of the unpredictability of the art, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

In response, applicants respectfully traverse the above "enablement" rejection. Without conceding the correctness of the Examiner's position, applicants note that claims 19-21 have been canceled, rendering the rejection thereof moot.

With regard to the rejection of claims 3-6, applicants note that that the legal standard for a lack of enablement, set forth in *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988), is a requirement for undue experimentation, i.e., experimentation that is not routine. In this context, the amount of experimentation required to practice an invention is irrelevant, the critical question being whether the experimentation required is routine. See *In re Wands*, 8 U.S.P.Q.2d 1400, 1404:

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. ... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed. The term "undue experimentation" does not appear in the statute, but it is well established that enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. ... Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the Board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. (emphasis added, footnotes omitted)

Applicants note also that "it is not necessary that a court review all of the *Wands* factors to find a disclosure enabling. They are illustrative, not mandatory." *Amgen v. Chugai Pharmaceutical*, 927 F.2d 1200, 1213 (Fed. Cir. 1991). As discussed below, applicants maintain that a sufficient number of the *Wands* factors are satisfied to establish that the specification is enabling for the invention being claimed.

Applicants note again the Examiner's statement of "the unpredictability in the art of administering undefined and uncharacterized compounds for the treatment of cardiovascular disease and cancer." In response, applicants respectfully disagree with the Examiner's position. Applicants maintain that the compounds are not undefined and uncharacterized, but instead are functionally defined as compounds which increase $p27^{kipl}$ activity, wherein the increase in $p27^{kipl}$ activity inhibits smooth

muscle cell migration. Thus, of the virtually infinite number of compounds in existence, the claims specify only a select few which exhibit the property of increasing intracellular $p27^{kip1}$ activity and thereby inhibiting smooth muscle cell migration.

Regarding the unpredictability of the art, the Examiner cites Koeffler (2003) which discloses that PPARγ ligands generally exhibit anti-cancer activity, but that murine models have suggested that these compounds may "paradoxically, ... under selected circumstances, ... stimulate cancer formation" (see abstract). The Examiner asserts that this evidence underlines the unpredictability that exists in the art.

In response, applicants note that it is in fact the norm that therapeutic agents have undesirable side effects. The alleged harmful side effects of successful COX-2 inhibitor drugs like Merck's Vioxx and Pfizer's Celebrex are typical examples. Indeed, it is not at all unusual that under selected conditions, therapeutic agents may exacerbate the condition they are used to treat. For example, nasal decongestants such as oxymetazoline and phenylephrine (active ingredients in popular brands such as Afrin and Sinex nasal sprays, respectively), are recommended for use for no more than 3-5 days since longer use leads to chronic "rebound congestion" (see **Exhibit A**, page 1 from article on "Decongestants for Sinusitis," available online at http://www.questdiagnostics.com/kbase/topic/detail/drug/hw59972/detail.htm).

Applicants maintain, however, that the mere possibility of undesirable side effects of a therapeutic occurring under selected conditions does not render the art so unpredictable as to negate the utility or patentability of a method of treatment. Applicants acknowledge that the occurrence of undesirable side effects may prevent an agent from being approved for treatment of human subjects. However, applicants emphasize that

considerations of safety and potential toxicity of therapeutics need not be addressed regarding patentability, and instead are the concern of the Food and Drug Administration. See *Scott v. Finney*, 32 U.S.P.Q. 2d 1115, 1120 (Fed. Cir. 1994):

> Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA) ... Congress has given the responsibility to the FDA, not to the [PTO], to determine ... whether drugs are sufficiently safe ... (citations omitted)

In addition, applicants note that claims 3 and 5, as amended herein, specify that the claimed methods of treatment result in an increase in $p27^{kipl}$ activity, and further note that this increase in $p27^{kipl}$ activity inhibits smooth muscle cell migration. Thus, applicants disagree with the Examiner's position that "it is impossible to predict what if any therapeutic effect the administration of any of these molecules would have ..." On the contrary, applicants maintain that one skilled in the art would predict that a treatment which inhibits smooth muscle cell migration would likely be effective in treating disorders characterized by increased smooth muscle cell migration.

With regard to the specific *Wands* factors, applicants note that the specification provides extensive guidance for identifying compounds that increase intracellular $p27^{kipl}$ activity and consequently inhibit cellular migration. See, e.g., page 19, line 27 to page 20, line 7, and page 20, line 21 to page 21, line 13 for methods of contacting cells with compounds; page 21, line 20 to page 22, line 9, and page 23, lines 16-20 for a method of estimating the intracellular level of $p27^{kipl}$ activity by assaying $p27^{kipl}$ protein levels.

Applicants note that these methods may require considerable

effort in screening a large number of compounds. Nonetheless, applicants assert that this is merely routine screening. Indeed, applicants note that the screening of large numbers of compounds is the norm in the pharmaceutical industry for identifying new candidate drugs. In addition, applicants reiterate that the specification provides ample guidance with respect to how this screening should be conducted. Applicants maintain, therefore, that based on *Wands*, the amount of experimentation required is permissible.

Further, applicants note that the specification provides at least two examples of compounds that satisfy the properties specified in the instant claims, as amended. These examples include rapamycin (see the specification at page 22, line 22 to page 25, line 13 and Figures 1-3) and C3 exoenzyme (see page 25, line 15 to page 26, line 5 and Figure 4). *Wands* does not specifically define what constitutes a sufficient number of examples. Applicants note, however, that a single example of an embodiment of the invention may suffice to show enablement provided that "any gaps between the disclosures and the claim breadth could be easily bridged." *Amgen v. Hoechst*, 314 F.3d 1313, 1336 (Fed. Cir. 2003). In the context of the present application, applicants respectfully submit that the disclosure in the specification of at least two examples of compounds with the activities specified in the claims suffices to show enablement of these claims. Moreover, applicants maintain that a skilled practitioner would be aware of, or would readily be able to identify, other compounds having the specified activities. For example, $p27^{kip1}$ protein itself and nucleic acids encoding this protein are compounds capable of increasing or causing an increase of intracellular $p27^{kip1}$ activity and thus inhibiting cell migration.

Regarding the relative skill of those in the art, applicants note

that the level of skill in the biological arts is very high. See, for example, *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, (Fed. Cir. 1999):

> [T]he district court determined that a person of ordinary skill in the art would be 'a junior faculty member with one or two years of relevant experience or a postdoctoral student with several years of experience,' *see Enzo*, 14 F.Supp.2d at 567, and we discern no clear error in this determination.

Applicants assert that the high level of skill in the art is a favorable factor in assessing the sufficiency of the specification in providing an enabling disclosure.

As noted above, applicants maintain that a skilled practitioner would reasonably predict that a treatment which inhibits smooth muscle cell migration will be effective in treating disorders characterized by enhanced smooth muscle cell migration. Applicants maintain that such a prediction is not undermined by the mere possibility that a compound which generally exhibits one property, may under selected circumstances exhibit a contrary property.

Further, applicants maintain that the claims are not overly broad. Applicants reiterate that the compounds specified in the instant claims, as amended herein, are not an "undefined" "plethora of compounds" as they have been characterized by the Examiner. Instead, applicants maintain that the compounds have clearly defined biochemical activities, and detailed guidance for identifying compounds exhibiting these activities is provided in the specification.

Based on the above analysis, applicants maintain that one skilled in the art would be able to practice the claimed invention without undue experimentation. Accordingly, applicants further maintain that the claims, as amended herein, are enabled by the

specification as filed. The Examiner is therefore respectfully requested to reconsider and withdraw the "enablement" rejection of the pending claims.

Rejections under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 19-21 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner stated that the recitation of the phrase "under conditions suitable for increasing p27 activity" in claims 19 and 21 is indefinite as it is not clear what conditions are deemed appropriate or conducive to increasing this activity.

In response, without conceding the correctness of the Examiner's position, applicants note that claims 19-21 are canceled, thereby rendering the above rejection moot.

Rejections under 35 U.S.C. §102(b)

Claims 3-6 and 19-21

The Examiner rejected claims 3-6 and 19-21 under 35 U.S.C. §102(b) as allegedly anticipated by PCT International Publication No. WO 99/65939.

The Examiner noted applicants' argument that WO 99/65939 is directed solely to methods of inhibiting cell proliferation, whereas the subject application provides method for inhibiting cell migration (citing page 18, second paragraph of applicants' May 27, 2005 Amendment). The Examiner also noted applicants' point that cell proliferation and cell migration are clearly distinct phenomena.

The Examiner responded that WO 99/65939 discloses methods for modulating, i.e., enhancing the activity of a p27(Kip1).FKBP-12 complex (citing page 9, lines 24 and 25). The Examiner stated that consequent to the enhancement of this intracellular cyclin-dependent kinase inhibitor p27 activity, there is cell cycle arrest and control of physiological processes such as hyperproliferative disorders, atherosclerosis and cardiac and muscle disease (citing page 9, lines 24-32). The Examiner also stated that the role of the cyclin kinase inhibitor p27(Kip1) is clearly implicated in artherosclerosis, tumorigenesis, tumor progression and spread (citing page 7, lines 9-11). The Examiner further stated that tumor spread is known to be the migration of cancer cells from one site (i.e., part of the body) to another site. The Examiner asserted that the invention disclosed in WO 99/65939 provides a method for treatment or prevention of various diseases and disorders, such as those related to organ transplantation, tumor spread, autoimmune diseases and atherosclerosis by administration of a therapeutic compound that modulates, i.e., promotes p27(Kip1).FKBP-12 (citing page 27, lines 10-29; page 33, lines 3-5). The Examiner also stated that the administration of these compounds upregulates p27 activity and thereby alleviates cardiovascular disease, inhibits tumor metastasis and inherently increases C3 exoenzyme activity.

In addition, the Examiner stated that WO 99/65939 discloses protein-protein interaction assays for assaying and screening derivatives, fragments, analogs and homologs of FKBP-12 for binding to p27(Kip1) in order to detect compounds that increase p27 activity, and after the identification of these compounds, they are administered (citing page 46, line 30 to page 47, line 20; page 48, line 9 to page 49, line 15; and page 50, line 31 to page 53, line 26).

In response, without conceding the correctness of the Examiner's

position, applicants note that claims 19-21 are canceled, rendering the rejection thereof moot.

Regarding the rejection of claims 3-6, applicants respectfully traverse this rejection. Without conceding the correctness of the Examiner's position, applicants note that the instant claims, as amended herein, specify that the compound which inhibits cell migration is administered to the subject in dosages of at least 4 mg/kg/day or, in one case, at least 9 mg/kg/day. Applicants note that WO 99/65939 discloses dosages at page 50, line 31 to page 51, line 9. However, none of the dosages disclosed in WO 99/65939 corresponds to the dosages recited in the instant claims, as amended.

Applicants note that a finding of anticipation requires a prior art reference to disclose each and every element of the claimed invention. Since WO 99/65939 does not disclose the specific dosages recited in the instant claims, as amended, applicants maintain that the rejection of claims 3-6 as anticipated by WO 99/65939 is unfounded. Applicants therefore respectfully request that this rejection be withdrawn.

Claims 3-6

The Examiner rejected claims 3-6 under 35 U.S.C. §102(b) as allegedly anticipated by PCT International Application No. WO 99/03508.

The Examiner noted applicants' prior argument that this rejection is directed exclusively to arresting cell growth and that the Examiner's conclusion that inhibition of cell growth is concurrent with the prevention of cell migration is incorrect.

The Examiner stated in response that WO 99/03508 discloses

methods for treating and preventing vascular proliferative diseases *in vivo* including restenosis, artherosclerosis and angiogenesis with a mutated p27, or a p27 fused with thymidine kinase (citing page 4, lines 6-15, and pages 30 and 31, claims 1-16). The Examiner further stated WO 99/03508 also discloses a method for providing a gene composition which expresses p27 in a therapeutically effective amount to a patient with a vascular proliferative disease, such as atherosclerosis, angiogenesis and restenosis (citing page 4, lines 7-21; page 10, line 11 to page 12, line 2). The Examiner asserted that the inhibition of cellular migration is inherent in the treatment of these diseases. The Examiner noted that the disclosed medicaments upregulate p27 activity. The Examiner also asserted that the increase/enhancement of cyclin-dependent kinase inhibitor p27 activity is, moreover, inherently due to the increase of C3 exoenzyme activity.

In response, applicants respectfully traverse this rejection. Without conceding the correctness of the Examiner's position, applicants note that the instant claims, as amended, specify that the compound which inhibits cell migration is administered to the subject in dosages of at least 4 mg/kg/day or, in one embodiment, at least 9 mg/kg/day. Applicants note that WO 99/03508 discloses the amount of p27 to be administered to a subject at page 10, line 19 to page 11, line 12. However, WO 99/03508 does not teach the dosages recited in the instant claims, as amended.

Thus, applicants note that WO 99/03508 does not disclose each and every element of the presently claimed invention. Accordingly, applicants maintain that this reference does not anticipate the claimed invention. Applicants respectfully request, therefore, that the rejection of claims 3-6 as anticipated by WO 99/03508 be withdrawn.

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 3-6 and 19-21 under 35 U.S.C. §102(a) as allegedly unpatentable over PCT International Publication No. WO 99/03508, and further in view of PCT International Publication No. WO 99/65939.

The Examiner stated that WO 99/03508 does not teach the methodology used to identify the compound that inhibits cellular migration. The Examiner also stated that WO 99/03508 does, however, teach protein-protein interaction assays for assaying and screening compounds for binding to p27(Kip1) in order to detect compounds that increase p27 activity, and after the identification of these compounds they are administered (citing page 46, line 30 to page 47, line 20; page 48, line 9 to page 49, line 15; page 50, line 31 to page 53, line 26). The Examiner asserted that it would have been *prima facie* obvious at the time the claimed invention was made to implement an assay to quickly and efficiently identify compounds that modulate p27 activity. The Examiner further stated that one of ordinary skill in the art would have been motivated to use the teachings of both documents with a reasonable expectation of success because WO 99/65939 established a screening assay, and WO 99/03508 established studies determining the effect of cyclin-dependent kinase inhibitors (citing Example 5 on pages 24 and 25).

In response, without conceding the correctness of the Examiner's position, applicants note that claims 19-21 are canceled, rendering the rejection thereof moot.

Regarding the rejection of claims 3-6, applicants respectfully traverse this "obviousness" rejection. Applicants note that, according to M.P.E.P. §2142, the Examiner bears the initial burden of factually establishing a *prima facie* case of

obviousness, and to do so, three basic requirements must be satisfied. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge of a skilled artisan, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference, or references when combined, must teach or suggest all the claim limitations.

Applicants maintain that the Examiner has failed to establish a *prima facie* case of obviousness. In this regard, applicants note that, as discussed above, the claimed invention specifies that the compound which inhibits cell migration is administered to the subject in dosages of at least 4 mg/kg/day or, in one embodiment, at least 9 mg/kg/day. Applicants reiterate that neither WO 99/03508 nor WO 99/65939 teaches or suggests this element of the claimed invention. Accordingly, applicants maintain that the Examiner has failed to satisfy at least one prong of the requirements for establishing a *prima facie* case of obviousness. Applicants therefore respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Conclusion

In view of the remarks made herein, applicants respectfully submit that the grounds of rejection set forth in the May 13, 2005 Final Office Action have been overcome. Accordingly, applicants respectfully request that the Examiner withdraw the rejections, and earnestly solicit allowance of all claims pending in the subject application.

If a telephone conference would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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